VIEWPOINT

Neurology and COVID-19

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In the early days of the coronavirus disease 2019 (COVID-19) pandemic, involvement by neurologists seemed unnecessary. The virus was thought to lead to a respiratory illness, largely sparing the brain and the rest of the nervous system. However, early reports from large outbreaks in China quickly changed this view. A study of more than 200 patients hospitalized in 3 COVID-19–focused hospitals in Wuhan demonstrated that more than one-third experienced a variety of neurologic manifestations, including altered mental status and acute cerebrovascular diseases, most commonly in those with severe respiratory illness.[1] These findings quickly changed the perspective of neurologists worldwide and focused efforts toward both understanding the mechanisms responsible for this neurologic involvement and devising systems of care to identify and effectively treat these increasingly recognized complications.

Multiple studies have demonstrated that patients with COVID-19 may develop ischemic stroke, although the exact frequency and risk factors remain unclear. While some reports have described a small number of patients with mild forms of the virus, most cases occur in those who are otherwise moderately or severely ill. Systemic illness alone does not seem to explain this association; in one study, the risk of ischemic stroke in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (n = 31 patients) was higher than in patients with seasonal influenza (n = 3 patients) (1.6% vs 0.2%; odds ratio, 7.6; 95% CI, 2.3-25.2).[2] Mechanisms of stroke in COVID-19 are likely numerous. The hypercoagulability that accompanies severe forms of the disease is likely a major driver, as are coexisting cardiac complications that lead to central embolic sources.

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Management of patients with COVID-19 and stroke remains an area in need of further investigation. Hospital protocols that screen for and quickly recognize stroke are complicated by coexisting respiratory and other complications in these patients, which may require deep sedation in those who are critically ill, obscuring recognition of neurologic changes. Stroke networks, designed to rapidly triage patients to centers where acute stroke treatments including thrombectomy can be rapidly performed, have been disrupted by fractured transfer protocols in hospital systems stretched to the limit at the height of the pandemic. Secondary prevention strategies including antithrombotic medications may need to be modified in patients who increasingly present with both clotting and hemorrhagic complications.

Despite the increased recognition of stroke as a complication of COVID-19, stroke hospitalizations have decreased substantially in the United States and in other countries during the pandemic, as demonstrated by multiple regional reports and an analysis of a national radiology data set of computed tomography perfusion software use.[3] This decline in patients presenting with stroke, which as yet has no clear explanation, has accompanied an overall decrease in emergency department visits nationwide in the US and likely represents, in part, patients not seeking care for acute neurologic symptoms, perhaps driven by concern about contracting infection during interactions with the health care system. The effect of this delayed cerebrovascular care is difficult to quantify, but given substantial improvement in the management of acute stroke, it likely will leave a lasting effect on health that neurologists will need to manage for years to come.

A nonspecific confusional state has increasingly been described in hospitalized patients with COVID-19, especially among older patients and those with severe disease. These patients share common risk factors for hospital-acquired delirium, and these cognitive complications are likely underrecognized in the setting of critical illness. While the etiology of this encephalopathy is probably multifactorial, the possibility of long-term cognitive effects will need to be addressed as with other causes of delirium, potentially leading to a major public health issue long after the pandemic has ended. In rare case reports, some of these patients have been diagnosed as having encephalitis, either infectious or postinfectious in etiology. However, in most patients who have undergone intensive investigation, spinal fluid analysis has not demonstrated inflammation, and polymerase chain reaction has not identified SARS-CoV-2 viral DNA in cerebrospinal fluid. Most reports of brain autopsy have not shown a robust inflammatory or viral infiltrate in cases of COVID-19, but rather, mainly signs of the influence of systemic hypoxia as well as occasional endothelial dysfunction and microthrombi.[4]

Neurologic complications have not been limited to the central nervous system (CNS). Like other SARS viruses, reports of SARS-CoV-2 neuromuscular complications have emerged, including cases of presumably postinfectious Guillain-Barré syndrome and a muscle disorder characterized by myalgias and elevated

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creatine kinase levels in serum.[1] While less common than CNS manifestations, peripheral nervous system involvement is more likely to be underreported, requiring further studies of patients using electrophysiology as well as neuropathology of nerve and muscle to determine the true incidence and characteristics of these manifestations.

Many crucial questions still remain to be answered in these early stages of understanding the neurology of COVID-19. Perhaps most important, discerning the extent and frequency of direct viral involvement of the nervous system will have wide-ranging implications on treatment approaches as well as prediction of any long-lasting effects of the illness. Currently, it is thought that most neurologic complications are due to systemic effects of the disorder, including cytokine release, immune-mediated inflammatory syndromes, and hypercoagulability; however, if a substantial proportion of patients have active virus in the CNS, treatments of these neurologic conditions will need to be designed with good CNS penetrance in mind.

There is reason to suspect that CNS viral involvement may potentially occur. The well-described loss of smell reported by many patients with SARS-CoV-2 infection likely represents direct viral involvement of the nasal epithelium, a structure on the "doorstep" of the CNS. A report of involvement of the olfactory regions of the brain in a patient with anosmia and COVID-19 raises the possibility that the virus can directly involve the brain in some patients.[5] Viral invasion could occur through entry at the level of the olfactory nerve but also could take place via the vascular endothelium, by transsynaptic transfer across infected neurons, or by migration of white blood cells across the blood-brain barrier.[6] Additional neuropathological studies and novel approaches to identifying the virus in cerebrospinal fluid in vivo will be essential to further understanding mechanisms driving these neurologic manifestations as well as facilitating their early detection. Based on the rarity of encephalitic presentations and limited autopsy data reported thus far, it is hoped that direct viral invasion of the CNS will remain a rare feature of this disease.

While most studies to date have focused on modest-sized cohorts of COVID-19 patients with neurologic disorders, more comprehensive epidemiological studies are required in large populations to accurately quantify the incidence of these complications, especially because a preponderance of case reports and small case series have dominated dissemination to the public via the popular press. Designing longitudinal studies to follow up patients who have recovered from mild and severe forms of the illness will allow for better understanding of the long-term consequences of neurologic involvement. Delayed neuropsychological testing and advanced neuroimaging is needed to more fully investigate the mild to moderate cognitive impairment that has anecdotally emerged among some patients who have recovered from COVID-19.

As important as these questions of biology are to the understanding of COVID-19, the pandemic has focused neurologists on designing effective systems of care for patients with various neurologic disorders. Patients with multiple sclerosis and others with inflammatory neurologic conditions are traditionally treated with immunosuppressive medications. These individuals are likely at higher risk of more severe COVID-19 illness, and the neurologic community has educated these patients regarding continued treatment of their underlying illness while utilizing unique care delivery models including teleneurology to ensure that they are still receiving the necessary safe, longitudinal care they require.[7]

The pandemic has also once again made neurologists keenly aware of striking disparities of care in the field. Well-established differences in the rates and severity of conditions such as stroke, epilepsy, and dementia among patients with varied socioeconomic and ethnic backgrounds have been compounded by a pandemic that disproportionally affects many of these same groups. Neurologists are challenged more than ever to directly address these disparities to ensure the provision of equitable and outstanding care for all persons with diseases of the nervous system, regardless of their background.

The COVID-19 pandemic has placed neurologists squarely in the middle of a health care system that has at times been challenged to provide care for large numbers of patients with this emerging disease. While there are perhaps more neurologic questions than answers at this stage, the focus of academic neurologists and those in community practice needs to remain on rapidly and effectively understanding the mechanisms, diagnosis, and treatment of COVID-19–related neurologic syndromes during this generational health care crisis.

ARTICLE INFORMATION

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